Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

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METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Introduction to pathological anatomy. Intracellular parenchymal degenerations”

Duration: 3 hours

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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To equip students with scientific knowledge regarding parenchymal degenerations, as well as the necessary skills and abilities for studying the etiopathogenesis and structural-functional features of parenchymal degenerations. This will be achieved by analyzing the general characteristics of the degenerative process and its classification based on the predominant type of metabolic disorder (protein, fat, carbohydrate), the localization of changes (intracellular, extracellular, mixed), and the prevalence of the process (systemic and local). This will foster students' understanding of the initial mechanisms underlying the development of pathological processes.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The causes, mechanisms, and morphological features of typical general pathological processes;
- The etiology, pathogenesis, and morphology of diseases at different stages of their development (morphogenesis), the structural basis of recovery, complications, outcomes, and long-term consequences of diseases, as well as the causes and mechanisms of dying (thanatogenesis).

Be able to:

- Identify major general pathological processes and diseases using histological specimens under light microscopy;
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

Master:

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

The vital activity of any tissue occurs as a result of continuous metabolism. In some cases, metabolic disorders cause qualitative changes in tissues or organs, whereby the content of natural metabolites increases in the cell and intercellular substance, or substances of a different chemical or physical composition appear. Such changes are called degeneration. Degeneration is among the most ancient processes in phylogenesis and accompanies many pathological processes and diseases in both children and adults. Thus, the degenerative process is universal and constitutes a general pathological category. It can unfold at various levels of organization of living matter: organ, tissue, cell, and cellular ultrastructures. The multitude of causes (nutritional, infectious and toxic, neuroendocrine disorders, developmental defects of various systems) disrupts the regulatory activity of the central nervous and immune systems, thereby altering the normal metabolism of proteins, fats, carbohydrates, and vitamins.

During the session, students are invited to study the structural-pathogenetic changes in organs and tissues in parenchymal dysproteinoses, lipidoses, and carbohydrate degenerations; analyze the morphogenetic aspects of the development of specific types of parenchymal degenerations; and pay attention to rare cases of congenital storage diseases.

QUESTIONS

1. Pathological anatomy as a medical science: definition, goals, objectives, and methods.
2. Autopsy: clinical and anatomical analysis, importance in medical practice, and legal aspects.
3. Biopsy: definition, types, and methods for studying biopsy specimens. The value of modern morphological methods (histochemistry, immunohistochemistry, electron microscopy) in the life-time diagnosis of diseases.
4. Pathology of the cell nucleus: changes in the structure, size, shape, and number of nuclei; structure and size of the nucleoli; nuclear membrane; pathology of mitosis; chromosomal aberrations and chromosomal diseases.
5. Parenchymal protein degenerations (dystrophies). Definition. Classification. General mechanisms of development of degenerative processes.
6. Parenchymal lipid degenerations (lipidosis). Etiology. Pathogenesis. Morphology. Clinical examples.
7. Parenchymal carbohydrate degenerations. Etiology. Pathogenesis. Morphology. Clinical examples.
8. Storage diseases: Gaucher’s disease, Niemann-Pick disease, Pompe’s disease, McArdle disease, Gierke disease.

COURSE OF THE SESSION

Pathology, in medical terms, refers to a **state of abnormality** or **disorder** within the body's physiological processes, structures, or functions. This condition is marked by deviations from the typical or healthy state of an organism, leading to observable signs, symptoms, or clinical manifestations that signal an impairment in health or well-being.

As a **branch of medical science**, pathology involves the **comprehensive study of diseases**. It focuses on understanding the nature, causes, and effects of various diseases by examining the underlying mechanisms that disrupt normal bodily functions. Pathologists investigate how diseases alter bodily structures and functions, aiming to elucidate the origins and progressions of diseases.

The field of pathology encompasses several core areas, including the **examination of tissue samples**, understanding **cellular changes**, and **identifying pathological processes**. By analyzing deviations from normal physiological conditions, pathology provides insights into disease processes, aids in diagnosing illnesses, and helps in determining the appropriate treatment and management strategies.

Introduction

Pathology is the study of the causes and effects of disease or injury. In modern medical contexts, the term is often used more specifically to refer to "general pathology," a field that encompasses various specialties involved in diagnosing diseases.

Within the field of general pathology, **pathological anatomy** (also known as **anatomical pathology**) focuses on the structural or morphological changes that occur in tissues and organs due to disease. This specialty examines how diseases alter the physical structure of the body, providing critical insights into disease mechanisms and aiding in accurate diagnoses.

A physician who specializes in pathology is referred to as a **pathologist**. Pathologists play a crucial role in modern medicine by performing diagnostic tests, interpreting laboratory results, and providing essential information that guides patient management and treatment strategies.

Introduction

As a field of general inquiry and research, pathology addresses components of disease: cause, mechanisms of development (**pathogenesis**), structural alterations of cells and tissues (**morphologic changes**), and the consequences of changes (**clinical manifestations**).

In common medical practice, general pathology is mostly concerned with analyzing known clinical abnormalities and is conducted by experts in one of two major specialties, anatomical pathology and clinical pathology.

Further divisions in specialty exist on the basis of the involved sample types (comparing, for example, **cytopathology**, **hematopathology**, and **histopathology**),

organs (as in renal pathology), and physiological systems (oral pathology), as well as on the basis of the focus of the examination (as with forensic pathology).

- General pathology
- Systemic pathology

Braches of pathology

1) **Anatomical Pathology** (**Histopathology**): This branch involves the examination of tissues, cells, and organs under a microscope to diagnose diseases and determine the extent of tissue damage. It includes **surgical pathology** (examining tissue samples from surgeries) and **cytopathology** (studying cells shed or aspirated from the body).

2) **Clinical Pathology** (**Laboratory Medicine**): This branch involves the analysis of bodily fluids (blood, urine, cerebrospinal fluid, etc.) and other specimens to diagnose diseases and monitor patients' health. It includes clinical chemistry, hematology, immunology, and microbiology.

3) **Forensic Pathology**: Forensic pathologists investigate the cause of death in cases involving criminal activity, accidents, or unexplained deaths. They perform autopsies and gather evidence for legal purposes.

4) **Neuropathology**: This branch focuses on the study of diseases affecting the nervous system, including the brain and spinal cord. Neuropathologists analyze brain tissue to diagnose conditions like Alzheimer's disease, brain tumors, and neurological disorders.

5) **Dermatopathology**: Dermatopathologists specialize in diagnosing skin diseases by examining skin biopsies and relating the findings to clinical information. This branch involves the intersection of dermatology and pathology.

6) **Hematopathology**: Hematopathologists study diseases related to blood, bone marrow, and lymphatic systems. They diagnose conditions such as leukemia, lymphoma, and anemia.

7) **Molecular Pathology**: This field focuses on the molecular and genetic basis of diseases. Molecular pathologists analyze DNA, RNA, and proteins to understand how genetic mutations contribute to disease development and progression.

8) **Cytogenetics**: Cytogeneticists study chromosomes and their abnormalities. They analyze chromosomal changes to diagnose genetic disorders and certain types of cancer.

9) **Immunopathology**: Immunopathologists study the immune system's role in disease. They investigate conditions related to immune responses, allergies, autoimmune disorders, and immunodeficiency diseases.

10) **Pediatric Pathology**: Pediatric pathologists specialize in diagnosing diseases that affect children and infants, often working closely with pediatricians and other specialists.

11) **Renal Pathology**: This branch deals with diseases of the kidneys. Renal pathologists study kidney tissue to diagnose conditions like glomerulonephritis, kidney infections, and renal tumors.

12) **Pulmonary Pathology**: Pulmonary pathologists study diseases of the respiratory system, including lung infections, chronic obstructive pulmonary disease (COPD), and lung cancer.

Key aspects of Pathology

1) **Etiology**: This refers to the investigation of the causes that lead to the manifestation of diseases. Understanding the origins of a disease helps in identifying risk factors and potential triggers.

2) **Pathogenesis**: This involves examining the mechanisms that govern the progression of a disease. It focuses on how the disease develops and how it affects the body over time.

3) **Morphogenesis**: This pertains to the analysis of the morphological foundations underlying disease mechanisms. It involves studying structural changes in tissues and organs that result from pathological processes.

4) **Sanogenesis**: This includes understanding the various outcomes related to disease resolution or recovery, along with the mechanisms that facilitate healing and restoration of health.

5) **Disability Development**: Examination of how diseases lead to functional impairments or disabilities, affecting the patient's quality of life.

6) **Complications**: Evaluation of potential complications that can arise from a disease or its treatment, which may impact the overall health outcome.

7) **Tanatogenesis**: This involves the examination of mortality and the mechanisms involved in the process of death. It focuses on understanding how and why death occurs in the context of disease.

Key aspects of Pathology

Pathomorphosis refers to changes in the nature of diseases and their manifestations over time, which can include:

1) **Alterations in Morbidity and Mortality**: Changes in the frequency and outcomes of diseases, reflecting shifts in public health and disease patterns.

2) **Therapeutic Pathomorphosis**: Modifications in the clinical and morphological attributes of diseases resulting from the administration of medications. This includes understanding how treatments affect disease progression and presentation.

Levels of investigation

Organism level allows to see the disease of entire organism, its different manifestations and correlation of organs and systems.

Systemic level – the level of study of any system of organs and tissues, combined by common functions (for example: system of connective tissue, system of blood, digestive system).

Organ level allows revealing the changes of organs, which are distinguished macroscopically or sometimes only with use of microscopic methods.

Tissue and cellular levels – the levels of study of changed tissues, cells and intercellular mater with use of microscopic methods.

Sub cellular level – allows to observe using electron microscopic the changes of ultrastructures of cells and intercellular matter, which are the primary morphological features of disease.

Molecular level – disease study is possible due to use of some complex methods (electron microscopic, cytochemical and other).

Methods of Pathology

Pathological anatomy takes material for investigation from **autopsy, surgical operations, biopsy and experimental investigations**.

Autopsy determines the causes of patient death, peculiarities of disease course, effectiveness of medicine therapy, diagnostic methods, and makes up the statistics of mortality.

Biopsy gives the possibility to study initial changes of cells and tissues by electron microscopy, histochemical, immunohistochemical and enzymological methods, to study those initial changes of disease the clinical manifestations of which are absent due to development of compensatory adaptive processes.

Biopsy material is one of the main objects of investigation as for practical, as for theoretical pathological anatomy.

Autopsy

An autopsy, also known as a **post-mortem examination**, is a critical procedure that involves the systematic dissection of a body to determine the **cause of death** and examine any **disease or injury present**. Clinically, autopsies serve as a final diagnostic tool that allows physicians to confirm or clarify the cause of death, evaluate the accuracy of clinical diagnoses, and understand the progression of diseases. By meticulously analyzing the organs and tissues, pathologists can uncover conditions that were undiagnosed or misdiagnosed during the patient's life, contributing significantly to medical knowledge and improving future patient care.

From an anatomical perspective, autopsies provide an in-depth look at the body's internal structures and systems, which can be vital for understanding how diseases affect the body. The detailed examination can reveal the presence of abnormalities, such as **tumors**, **infections**, or **degenerative diseases**, that **might not have been evident** through non-invasive imaging techniques or other diagnostic tools. This anatomical analysis not only deepens our understanding of disease processes but also helps in identifying new pathological conditions, leading to advancements in medical research and treatment strategies.

The **importance** of autopsies in medical practice extends beyond individual patient care. They play a crucial role in **quality assurance** and **medical education**. For physicians and medical students, autopsies offer invaluable learning opportunities by **correlating clinical findings with actual pathological conditions**, thus enhancing diagnostic accuracy. Hospitals and medical institutions often use autopsy results to review the quality of care provided, identifying any **diagnostic or therapeutic errors**. This feedback loop is essential for improving clinical practice, patient safety, and overall healthcare outcomes.

Legally, autopsies are often mandated in cases of **unexplained**, **suspicious**, or **sudden deaths** to ascertain the cause of death and to rule out foul play. They are a key component in forensic investigations, providing crucial evidence that can influence the outcome of legal proceedings. **Forensic autopsies** differ from **clinical autopsies** in that they are conducted with a focus on determining whether a crime has been committed, and they are often requested by legal authorities. The findings of a forensic autopsy can be pivotal in **criminal cases**, **insurance claims**, and other legal matters, making them an indispensable tool in the intersection of medicine and law.

Incisions in autopsy

From a medical perspective, different types of autopsy incisions (or cuts) are used depending on the purpose of the autopsy, the area of the body being examined, and the specific procedures required.

1) **Y-Incision**: The Y-incision is the most commonly used incision in **full autopsies**. It starts from both shoulders, meeting at the sternum (breastbone), and then extends down to the pubic bone. This cut provides access to the chest and abdominal cavities, allowing the pathologist to examine major organs such as the heart, lungs, liver, kidneys, and intestines. The Y-incision is typically used in comprehensive autopsies where a thorough examination of the body's major internal organs is needed.

2) **I-Incision**: The I-incision is similar to the Y-incision but is **simpler**, with a single straight cut from the neck down to the pubic bone. This type of incision is often used in cases where a less extensive examination is required, or when the deceased has undergone prior surgeries or interventions that make the Y-incision impractical. The I-incision provides access to the thoracic and abdominal cavities, but with less exposure than the Y-incision.

3) **U-Incision**: The U-incision is used primarily in **cranial autopsies**, particularly when there is a need to examine the brain. This cut is made from one ear, across the top of the head, to the other ear, creating a U-shaped flap of scalp that can be pulled forward over the face. After making this incision, the skull is opened with a saw to access the brain. This approach is used in cases involving head trauma, neurological diseases, or when brain pathology is suspected.

Methods of autopsy

1) **Rokitansky Method**

Overview: The Rokitansky method, named after Karl von Rokitansky, is characterized by the in-situ dissection of the body. This means that the organs are examined in place within the body cavities before being removed.

Procedure: The organs are removed one by one or in small groups after initial in-situ examination. This method emphasizes systemic disease investigation by allowing the pathologist to observe the organs in their natural relationships and anatomical context.

Usage: It is particularly useful for examining the connections between organs and understanding the overall pathophysiology in cases of systemic disease.

2) **Virchow Method**

Overview: Named after Rudolf Virchow, the Virchow method involves the removal and examination of organs individually. Each organ is dissected and studied separately.

Procedure: Organs are removed one at a time, starting usually with the brain, followed by the thoracic and abdominal organs. Each organ is fully examined after removal.

Usage: This method is ideal for focusing on organ-specific diseases and conditions, allowing for detailed examination of each organ independently.

3) **Ghon Method**

Overview: The Ghon method, named after Anton Ghon, involves the removal of organs in regional blocks or organ complexes. This means that organs that are anatomically or functionally related are removed together.

Procedure: The body is divided into three main blocks or compartments: the thoracic organs (heart and lungs), the abdominal organs (liver, spleen, pancreas, intestines), and the urogenital organs. Each block is removed as a single unit and then dissected.

Usage: This method preserves the anatomical relationships between organs, making it useful for examining conditions that affect multiple organs within the same region.

4) **Letulle Method (Shor Method)**

Overview: The Letulle method, often referred to as the Shor method, involves the en masse removal of all the organs as a single block. This allows for a comprehensive examination of the body's organs in their entirety before dissection.

Procedure: All the thoracic, cervical, abdominal, and pelvic organs are removed together as one large block. Once removed, the organs are dissected systematically on the autopsy table.

Usage: This method is particularly valuable for maintaining the connections between organs, making it useful for understanding complex pathological processes that involve multiple systems.

Key Differences in Methods

1) **Rokitansky** focuses on in-situ examination with subsequent removal of organs in smaller groups or individually.

2) **Virchow** emphasizes the individual removal and dissection of each organ.

3) **Ghon** involves the removal of organs in regional blocks, maintaining their anatomical relationships.

4) **Letulle** (Shor) involves the en masse removal of all organs, maintaining their systemic relationships until they are dissected together outside the body.

Biopsy

A biopsy is a medical procedure in which a **small sample of tissue** is removed from the body for **diagnostic examination**. It is a critical tool in the diagnosis of diseases, particularly cancers, as it allows for the direct analysis of cells and tissues to determine their **structure**, **function**, and any **abnormalities**. By examining

biopsy specimens, pathologists can identify the presence of disease, assess its severity, and sometimes predict the likely outcome or best treatment approach. Biopsies are essential in confirming diagnoses that cannot be made based on clinical or imaging findings alone.

There are several types of biopsies, each suited to different medical situations.

Needle biopsies include **fine-needle aspiration** (FNA), which uses a thin needle to extract fluid or cells, and core needle biopsy, which removes a small cylinder of tissue.

Incisional biopsies involve the removal of a portion of the suspicious tissue, while **excisional biopsies** involve removing the entire area of interest, such as a lump or mass.

Endoscopic biopsies are performed using an endoscope, a flexible tube with a light and camera, to obtain tissue from internal organs like the stomach or lungs.

Punch biopsies are commonly used in dermatology, where a circular tool removes a small section of skin, while shave biopsies involve shaving off a thin layer of skin.

Once a biopsy sample is obtained, it undergoes various methods of analysis to provide a definitive diagnosis.

Histological examination is the most common method, where the tissue is fixed, sectioned, and stained for microscopic examination. **Histochemistry** involves the use of chemical reactions to identify specific tissue components, such as enzymes or lipids, which can provide insights into the metabolic state or specific types of cellular activity.

Immunohistochemistry (**IHC**) is a more advanced technique that uses antibodies to detect specific proteins within the cells. IHC is particularly valuable in identifying markers that are characteristic of certain types of cancer, infections, or other diseases, allowing for a more precise diagnosis.

Electron microscopy provides detailed images of cellular structures at a much higher resolution than light microscopy, making it useful for diagnosing diseases that involve ultrastructural changes, such as certain kidney diseases, muscle disorders, or viral infections.

Histochemistry allows for the **visualization of biochemical components** within tissues, which is crucial for diagnosing metabolic and storage diseases.

Immunohistochemistry has revolutionized the diagnosis of cancers and other diseases by enabling the **detection of specific antigens** that are not visible through standard histological techniques. This method is particularly important in oncology for distinguishing between different **types of tumors**, determining the **origin of metastatic cancers**, and identifying prognostic and therapeutic markers.

Electron microscopy remains an essential tool in diagnosing diseases that involve complex **structural changes at the cellular level**, providing insights that cannot be obtained through other methods.

Overview of nuclear pathology

The cell nucleus is a highly specialized organelle that plays a central role in maintaining cellular homeostasis. It houses the genetic material (DNA) and regulates

essential processes such as transcription, DNA replication, cell cycle progression, and apoptosis. Because of its crucial functions, the nucleus is particularly sensitive to pathological stimuli, and changes in its morphology often serve as early indicators of cellular injury, stress, or transformation. These changes can be observed in both non-neoplastic and neoplastic diseases, making nuclear morphology a key diagnostic feature in histopathology and cytopathology.

Clinical relevance:

1) Nuclear changes are essential diagnostic markers in **cancer pathology**.

2) Specific nuclear features help distinguish between **benign**, **premalignant**, and **malignant** cells.

3) Evaluation of nuclear pathology aids in assessing **prognosis** and **guiding therapy**, especially in tumors.

Pathological changes in nucleus

1) **Size**: Enlargement or shrinkage of the nucleus can indicate increased DNA content or impending cell death.

2) **Shape**: Irregular, lobulated, or deformed nuclei often suggest neoplastic transformation.

3) **Number of nuclei**: Multinucleation is seen in viral infections, certain physiological states, and malignancies.

4) **Nucleoli**: Their size, number, and appearance reflect protein synthesis activity and proliferative status.

5) **Nuclear membrane**: Integrity is essential for compartmentalization and gene regulation; its breakdown can signify degeneration or genetic disease.

6) **Mitosis and chromosomes**: Mitotic abnormalities and chromosomal defects underlie many genetic syndromes and cancers.

Nuclear morphology

Changes in nuclear morphology are often the first indicators of pathology.

Size and shape:

1) **Karyomegaly** (enlarged nuclei): often seen in cancer or viral infection.

2) **Karyopyknosis** (condensed nuclei): typical of apoptosis.

3) **Karyorrhexis** and **karyolysis**: fragmentation and dissolution in necrosis.

4) **Hyperchromasia**: dense, dark-staining chromatin — often malignant.

5) **Irregular nuclear contours**: suggest dysplasia or malignancy.

Number of nuclei (multinucleation) may occur:

- Physiologically in skeletal muscle, megakaryocytes.
- Pathologically in viral infections (e.g., HSV, CMV) and neoplasms.

Atypical nuclear numbers or arrangements point to mitotic dysfunction or transformation.

Nucleolar & nuclear membrane pathology

The nucleolus reflects the cell’s protein synthesis activity. The nuclear membrane maintains nuclear integrity and regulates nucleocytoplasmic exchange.

Nucleolar pathology:

1) Enlarged or multiple nucleoli: seen in active or transformed cells.

2) Prominent nucleoli in malignancy (e.g., Reed-Sternberg cells).

3) Disruption indicates increased proliferation or oncogenic stress.

Nuclear membrane changes:

1) Membrane blebbing or rupture → micronuclei formation.

2) Seen in laminopathies (e.g., Hutchinson-Gilford progeria).

3) Defective envelopes contribute to genomic instability.

Pathology of mitosis and mitotic figures

Mitosis is the process by which a cell divides its genetic material equally between two daughter cells. Proper mitotic division is crucial for maintaining genomic stability. Disruption of this process can lead to aneuploidy, polyploidy, or structural chromosomal abnormalities — all of which are commonly observed in malignant transformation.

Key mitotic abnormalities:

1) **Multipolar mitoses**: Instead of forming a bipolar spindle, the cell divides via three or more poles. This leads to unequal chromosome segregation.

2) **Lagging chromosomes**: Chromosomes that do not properly align or separate, often forming **micronuclei**.

3) **Mitotic arrest**: Cells are unable to complete mitosis due to damage or spindle defects — common in response to radiation or chemotherapeutic agents like taxanes and vinca alkaloids.

4) **Hypermitotic activity**: A high number of mitotic figures, especially abnormal ones, is a marker of aggressive tumors (e.g., high-grade sarcomas, carcinomas).

Pathological implications:

1) Faulty mitosis contributes to **genomic instability**, a hallmark of cancer.

2) Abnormal mitotic figures help pathologists grade tumors and assess their proliferative index.

3) Mitotic catastrophe may trigger cell death in response to genotoxic stress.

Chromosomal aberrations & diseases

Chromosomes are vulnerable to both structural damage and numerical errors, particularly during DNA replication or mitosis. These aberrations are central to many inherited syndromes, developmental defects, and cancers.

Structural chromosomal aberrations:

1) **Deletions**: Loss of chromosomal segments; e.g., 5p- syndrome (Cri-du-chat).

2) **Duplications**: Repetition of chromosomal segments, potentially disrupting gene dosage.

3) **Inversions and insertions**: Rearrangement of chromosomal parts can disrupt gene function.

4) **Translocations**: Exchange between nonhomologous chromosomes; e.g.:

- **t(9;22)** Philadelphia chromosome → BCR-ABL fusion gene in chronic myeloid leukemia.
- **t(14;18)** → BCL2 overexpression in follicular lymphoma.

Numerical abnormalities (aneuploidies):

1) **Trisomy 21 (Down syndrome)**: Intellectual disability, cardiac defects, increased leukemia risk.

2) **Trisomy 18 (Edwards syndrome)**: Severe developmental delay, poor survival.

3) **Monosomy X (Turner syndrome)**: Female phenotype with short stature, gonadal dysgenesis.

Micronuclei and chromothripsis:

1) **Micronuclei**: Small extranuclear bodies containing lagging chromosomes or fragments, often seen in genotoxic stress or cancer.

2) **Chromothripsis**: A catastrophic event causing hundreds of chromosomal rearrangements in a single mitosis — frequently observed in high-grade malignancies.

Clinical relevance:

Karyotyping and molecular cytogenetics (FISH, CGH, NGS) are critical for diagnosis, prognosis, and therapy selection in hematologic and solid tumors.

DEGENERATION (aka DYSTROPHY)

Degeneration is a pathological process arising from disturbances in cellular and tissue metabolism, ultimately culminating in morphological damage.

The causes of degeneration are:

- disruptions in cellular self-regulation
- malfunctioning of the body's transport systems (blood, lymph)
- imbalances in neurohumoral regulation of metabolism

There are **4 mechanisms** of degeneration development:

1. Infiltration.
2. Decomposition.
3. Abnormal synthesis.
4. Transformation.

Classification of Degeneration

1) Based on localization:

- Parenchymatous
- Mesenchymal
- Mixed

2) Depending on the predominant biochemical substance:

- Proteins
- Lipids
- Carbohydrates
- Pigments
- Minerals

3) According to the influence of genetic factors:

- Congenital (primary)
- Acquired (secondary)

4) Based on distribution:

- Localized
- Generalized

Parenchymal degenerations

Parenchymal degenerations occur when pathological changes primarily affect the parenchyma, or **functional cells**, of an organ. These changes often involve the abnormal accumulation of substances within the cell's cytoplasm or nucleus. Depending on the severity, intracellular accumulation can lead to either reversible or irreversible cell injury.

These abnormal intracellular accumulations can be categorized into three main groups:

1) Accumulation of normal metabolic products that are produced in excess.

2) Accumulation of abnormal substances resulting from metabolic dysfunction, often due to enzyme deficiencies.

3) Accumulation of pigments.

Based on the type of metabolic disturbance, parenchymal degenerations are further classified into **protein**, **lipid**, and **carbohydrate** degenerations.

Parenchymal protein degenerations

Pathologic accumulation of proteins in the cytoplasm of cells can occur under various conditions, each reflecting a different underlying mechanism.

For instance, in **proteinuria**, excessive proteins are reabsorbed by renal tubular cells, leading to their accumulation in the cytoplasm.

In plasma cells that are actively synthesizing immunoglobulins, the cytoplasm may contain pink hyaline inclusions known as **Russell's bodies**, which represent accumulated immunoglobulins.

Another example is **α1-antitrypsin deficiency**, where misfolded α1-antitrypsin proteins accumulate in hepatocytes, leading to liver damage.

Additionally, in chronic alcohol abuse, hepatocytes may exhibit **Mallory's bodies** or alcoholic hyaline, which are cytoplasmic inclusions composed of misfolded cytokeratin intermediate filaments.

Protein parenchymal degenerations can be classified into four distinct types:

1) **Granular degeneration**: Characterized by the accumulation of fine protein granules within the cytoplasm.

2) **Hydropic degeneration**: Marked by cell swelling due to the accumulation of water and proteins, leading to vacuolization.

3) **Hyaline-droplet degeneration**: Involves the presence of hyaline droplets within the cytoplasm, often seen in kidney and liver cells.

4) **Keratin degeneration** (**keratosis**): Involves abnormal accumulation and changes in keratin within epithelial cells, leading to conditions like keratosis.

Each of these types reflects a specific pattern of protein accumulation and cellular response, providing insight into the underlying pathology.

Granular degeneration

Granular degeneration is a reversible intracellular condition characterized by the **hyperplasia of cellular ultrastructures**, which occurs as a response to functional overstrain under various pathological influences. This condition reflects the cell's attempt to adapt to increased demands or stress.

Microscopically, the intracellular granules observed in granular degeneration are not actual protein granules, but rather represent **hyperplastic cellular ultrastructures**, such as mitochondria or endoplasmic reticulum, that have proliferated in response to the overstrain.

If the pathological stimulus continues, **granular degeneration can progress** to more severe forms of cell damage, such as hyaline-droplet or hydropic degeneration. These conditions represent further stages of cellular injury, and if the damaging influence persists, they may ultimately lead to cell necrosis, marking irreversible cell death.

Hydropic degeneration

Hydropic degeneration, also known as **vacuolar** or **balloon degeneration**, is characterized by the presence of **vacuoles filled with cytoplasmic fluid** within cells. This form of degeneration reflects severe cellular injury and is a critical indicator of impending cell death.

1) **Cell Swelling**: The affected cells become swollen, which can compress the surrounding microvasculature, disrupting local blood flow.

2) **Vacuoles**: Small, clear vacuoles appear within the cytoplasm, representing distended cisternae of the endoplasmic reticulum filled with fluid.

3) **Ultrastructural Changes**: These include the dilatation of the endoplasmic reticulum, detachment of polysomes from the surface of the rough endoplasmic reticulum (RER), mitochondrial swelling, the formation of blebs on the plasma membrane, and the loss of fibrillarity in the nucleolus.

Hydropic swelling is typically considered an **irreversible condition**. As the cellular damage progresses, it often culminates in either focal or total **colliquative necrosis**, leading to the complete breakdown and dissolution of the affected cells.

Hyaline-droplet degeneration

Hyaline is a histologic term used to describe a glassy, homogeneous, and **eosinophilic appearance** of material in hematoxylin and eosin-stained tissue sections. It is important to note that "hyaline" does not refer to a specific substance but rather to a characteristic appearance observed under the microscope.

Intracellular hyaline can be found in various organs, including the kidneys, liver, and, less commonly, in the myocardium and skeletal muscles.

This form of degeneration is **irreversible** and often leads to **coagulative necrosis**, a type of cell death characterized by the preservation of the basic cellular outline but with a loss of cellular detail and function.

Examples of hyaline-droplet degeneration

1) **Hyaline droplets** in the proximal tubular epithelial cells, typically seen in cases of excessive reabsorption of plasma proteins, such as in proteinuria.

2) **Zenker's degeneration**, which occurs in skeletal muscles, leading to the accumulation of hyaline material.

3) **Alcoholic hepatitis**, where hyaline inclusions, known as Mallory bodies, are observed in the liver cells.

4) **Viral infections**, where hyaline inclusions can be seen within the affected cells.

5) **Russell's bodies**, which are eosinophilic hyaline inclusions found in plasma cells, representing accumulated immunoglobulins.

Keratosis

Keratosis, or keratin degeneration, refers to the abnormal formation or **accumulation of keratin in epithelial tissues**. It can occur in several conditions, each reflecting different pathological processes:

1) **Hyperkeratosis** and **Ichthyosis**: These conditions involve an increased formation of keratin in normally keratinized epithelium. Hyperkeratosis is characterized by the thickening of the outer layer of the skin due to excessive keratin production, while ichthyosis refers to a group of disorders that cause dry, scaly skin due to abnormal keratinization.

2) **Leukoplakia**: This condition is marked by the formation of keratin in epithelial tissues that do not typically undergo keratinization, such as the mucous membranes. Leukoplakia presents as white patches and is often considered a precancerous condition due to the abnormal keratinization process.

3) **Keratinization in Epithelial Tumors**: In squamous cell carcinoma, a type of epithelial tumor, abnormal keratin formation can occur, leading to the development of keratin "pearls." These are concentric layers of keratin found within the tumor and are a hallmark of this type of cancer.

Parenchymal lipid degenerations

Fatty change, also known as **steatosis** or fatty metamorphosis, is characterized by the intracellular accumulation of neutral fat within parenchymal cells. This condition reflects an increase in the amount of lipids within the cell's cytosol, or cytoplasmic matrix.

The term "**fatty change**" encompasses what were previously known as **fatty degeneration** and **fatty infiltration**, though these terms are now considered outdated. Unlike these older terms, fatty change does not necessarily involve cellular degeneration or infiltration. Instead, it specifically denotes an absolute increase in intracellular lipids.

While fatty change is most commonly observed in the **liver**, it can also occur in other non-fatty tissues such as the heart, kidneys, skeletal muscle, and various other organs. The accumulation of fat in these tissues is due to the deposition of lipid droplets in the cytoplasm.

One of the primary causes of fatty change is **oxygen insufficiency** (**hypoxia**). This can result from conditions such as cardiovascular diseases, anemia, or lung diseases, which impair the oxygen supply to tissues. Additionally, **intoxication** from substances like alcohol or certain toxins can also lead to fatty degeneration by disrupting lipid metabolism and transport.

Heart lipid degeneration

In cardiomyocytes, the accumulation of lipids causes a significant dystrophic change. As these lipids accumulate, they displace the cytoplasm of the cells. If the process is mild, the external appearance of the organ may remain unchanged. However, in more severe cases, the affected heart becomes noticeably altered.

In severe instances of fatty change in the heart, the organ becomes flabby and enlarged. Upon dissection, the heart tissue exhibits a yellowish coloration due to the lipid deposits. Additionally, the endocardium, particularly in the papillary muscles, may display distinct yellow-white striations. These visual changes are indicative of the extent of lipid accumulation and reflect the degree of pathological alteration in the heart tissue.

Liver steatosis

The liver is the most common site for fat accumulation due to its central role in fat metabolism. Fatty liver, or hepatic steatosis, can arise from a variety of causes, each impacting the liver's ability to process and manage lipids effectively.

1) **Excess Alcohol Consumption**: Chronic alcohol intake disrupts normal lipid metabolism in the liver, leading to the accumulation of fat within liver cells.

2) **Starvation**: Prolonged starvation or fasting causes the mobilization of fatty acids from adipose tissue, which are then delivered to the liver and can overwhelm its capacity to metabolize them.

3) **Malnutrition**: Inadequate nutrient intake can impair liver function and fat metabolism, leading to the accumulation of fat in liver cells.

4) **Obesity**: Excessive body weight increases the risk of developing fatty liver, as the liver becomes overloaded with fatty acids derived from adipose tissue.

5) **Diabetes Mellitus**: Insulin resistance and elevated blood glucose levels associated with diabetes can lead to increased fat accumulation in the liver.

6) **Chronic Illnesses**: Various chronic diseases can impair liver function and fat metabolism, contributing to the development of fatty liver.

7) **Late Pregnancy**: Fatty liver can occur during late pregnancy, often referred to as acute fatty liver of pregnancy, which is a serious condition that requires medical attention.

8) **Hypoxia**: Reduced oxygen levels can impair liver cell function and lipid metabolism, leading to fat accumulation.

9) **Hepatotoxins**: Exposure to toxins that damage liver cells can disrupt lipid metabolism and result in fatty liver.

10) **Certain Drugs**: Medications such as corticosteroids and some chemotherapeutic agents can contribute to the development of fatty liver as a side effect.

11) **Reye's Syndrome**: This rare but serious condition, often following a viral infection, is associated with fatty liver and other severe liver dysfunctions.

Even in severe cases of liver cell dysfunction, such as those resulting from chronic alcohol consumption, the **damage may be reversible**. For example, if an individual with severe fatty liver but without progressive fibrosis or cirrhosis stops drinking alcohol, the liver can return to normal over time, given appropriate lifestyle changes.

Grossly, a fatty liver is notably **enlarged** and has a tense, glistening capsule with rounded margins. The cut surface of the liver bulges slightly and appears **pale yellow** to yellow. It feels **greasy** to the touch due to the accumulation of lipids.

Microscopically, fatty liver is characterized by numerous **lipid vacuoles** within the cytoplasm of hepatocytes. Initially, these vacuoles are small and distributed around the nucleus, referred to as **microvesicular steatosis**. As the condition progresses, the vacuoles enlarge, pushing the nucleus towards the periphery of the cell, resulting in **macrovesicular steatosis**. In severe cases, hepatocytes filled with large lipid vacuoles may rupture, leading to the coalescence of vacuoles into fatty cysts.

To visualize fat within liver tissue, special staining techniques are employed. Frozen sections of the tissue are prepared and then stained with fat-specific dyes such as Sudan dyes (**Sudan III, Sudan IV**), Sudan black, **oil red O**, or **osmic acid**. These stains highlight the presence of lipids, facilitating the assessment of fatty changes in the liver.

Cholesterol degeneration

Intracellular deposits of cholesterol and its esters in macrophages can occur in conditions of **hypercholesterolemia**, leading to the transformation of these macrophages into **foam cells**. This process is associated with various pathological conditions, including:

1) Fibrofatty Plaques of **Atherosclerosis**: In atherosclerosis, cholesterol and its esters accumulate in the arterial wall, where they are taken up by macrophages. These macrophages become foam cells, contributing to the formation of fibrofatty plaques. These plaques can lead to the narrowing and hardening of arteries, increasing the risk of cardiovascular events.

2) **Xanthomas** and **Xanthelasma**: Xanthomas are tumor-like masses that form in the skin or other tissues due to cholesterol deposition. They appear as clusters of foam cells and are often associated with lipid metabolism disorders. Similarly, xanthelasma are yellowish plaques that occur on the eyelids or around the eyes, resulting from the accumulation of cholesterol in macrophages. Both xanthomas and xanthelasma are indicative of underlying hypercholesterolemia and lipid dysregulation.

Parenchymal carbohydrate degeneration

1) **Diabetes Mellitus**: In diabetes mellitus, whether due to an absolute or relative deficiency of insulin, the cellular uptake of glucose is impaired. As a result, glucose cannot be efficiently converted into glycogen for storage. Instead, it

accumulates intracellularly in various tissues. This abnormal accumulation of glycogen occurs because the cells are unable to properly manage glucose due to insufficient insulin action.

2) **Glycogen Storage Diseases** (**Glycogenosis**): These are a group of inherited disorders caused by genetic defects affecting the metabolism of glycogen. Each type of glycogen storage disease involves a specific enzyme deficiency that disrupts glycogen breakdown or synthesis, leading to the accumulation of glycogen in various tissues. This accumulation can result in organ enlargement, dysfunction, and a range of clinical symptoms depending on the specific type of glycogen storage disease.

3) **Glycoprotein Metabolism Disturbances**: Disorders involving the metabolism of glycoproteins lead to the accumulation of mucins and mucous-like substances within cells. These disturbances can result in conditions such as mucopolysaccharidoses, where abnormal accumulation of glycosaminoglycans occurs. This accumulation affects tissue function and can lead to various systemic and organ-specific manifestations.

Storage diseases

In storage diseases, hereditary factors lead to metabolic disturbances resulting in the abnormal accumulation of various substances within cells. These conditions are commonly referred to as storage diseases or **enzymopathies**, reflecting their basis in enzyme deficiencies or dysfunctions that disrupt normal metabolic processes.

Most storage diseases are classified as **lysosomal storage diseases**, where defective lysosomal enzymes impede the breakdown of substrates, leading to their accumulation within lysosomes. These diseases are typically inherited through **autosomal recessive or sex-linked** (X-linked recessive) genetic patterns, meaning that they require two copies of the defective gene (in autosomal recessive cases) or one defective gene on the X chromosome (in X-linked recessive cases) for the disease to manifest.

Storage diseases are categorized based on the type of metabolic disturbance they cause:

1) **Proteinosis**: This group involves the abnormal accumulation of proteins within cells. Examples include certain types of proteolytic enzyme deficiencies that lead to the buildup of abnormal protein products.

2) **Lipidosis**: This category refers to disorders involving the accumulation of lipids or fats. Examples include **Gaucher's disease**, **Tay-Sachs disease**, and **Niemann-Pick disease**, where specific lysosomal enzymes responsible for lipid breakdown are deficient or dysfunctional.

3) **Glycogenosis**: This group consists of diseases related to abnormal glycogen metabolism. In these conditions, such as **Pompe disease** and **McArdle disease**, glycogen accumulates in tissues due to defects in enzymes responsible for glycogen synthesis or degradation.

Gaucher's disease

This is an autosomal recessive disorder in which there is a deficiency of lysosomal enzyme, glucocerebrosidase, which normally cleaves glucose from ceramide. This results in lysosomal accumulation of glucocerebroside (ceramide-glucose) in phagocytes of the body and sometimes in the neurons.

Clinically, there are 3 types of Gaucher's disease:

1. **Type I** or classic form is the adult form of the disease in which there is storage of glycocerebrosides in the phagocytes of the body, principally involving the spleen, liver, bone marrow and lymph nodes. This is the most common type comprising 80% of all cases of Gaucher's disease.

2. **Type II** is the infantile form in which there is progressive involvement of the central nervous system.

3. **Type III** is the juvenile form of the disease having features in between type I and type II, i.e. they have systemic involvement like in type I and progressive involvement of the central nervous system (CNS) as in type II.

Gaucher's disease

In addition to involvement of different organs and systems (splenomegaly, hepatomegaly, lymphadenopathy, bone marrow and cerebral involvement), a few other features include pancytopenia, or thrombocytopenia secondary to hypersplenism, bone pains and pathological fractures.

Microscopically, large number of characteristically distended and enlarged macrophages called Gaucher cells are found in the spleen, liver, bone marrow and lymph nodes, and in the case of neuronal involvement, in the Virchow-Robin space. The cytoplasm of these cells is abundant, granular and fibrillar resembling crumpled tissue paper.

Niemann-Pick disease

It is an autosomal recessive disorder characterized by accumulation of sphingomyelin and cholesterol.

The condition presents in infancy and is characterized by **hepatosplenomegaly**, **lymphadenopathy** and physical and mental underdevelopment.

The cells of Niemann-Pick disease are somewhat smaller than Gaucher cells and their cytoplasm is not wrinkled but is **foamy** and **vacuolated** which stains positively with fat stains. These cells are located in the spleen, liver, lymph nodes, bone marrow, lungs, intestine and brain.

Glycogenosis

Pompe's disease is also an autosomal recessive disorder due to deficiency of a lysosomal enzyme, acid mahase. Its deficiency results in accumulation of glycogen in many tissues, most often in the **heart and skeletal muscles** leading to cardiomegaly and hypotonia.

McArdle disease occurs due to deficiency of muscle phosphorylase resulting in accumulation of glycogen in the **muscle** (deficiency of liver phosphorylase).

Gierke Disease is an inherited autosomal recessive disorder due to eficiency of enzyme glucose-6-phosphatase. The disease manifests clinically in infancy with

failure to grow and stunted growth. Most prominent feature is **enormous hepatomegaly** with intracytoplasmic and intranuclear parenchymatous glycogen. The **kidneys are also enlarged** and show intracytoplasmic glycogen in tubular epithelial cells.

The outcome of storage diseases is **unfavorable** because of its insufficiency of the respective organ.

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